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SEMINAR ON CONTRAST TWO-DIMENSIONAL ECHOCARDIOGRAPHY: APPLICATIONS AND NEW DEVELOPMENTS. PART III*

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Guest Editors

Computer Methods for Myocardial Contrast Two-Dimensional Echocardiography

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Two computer-aided videodensitometric methods that may be used in conjunction with two-dimensional contrast echocardiography were examined to quantify the time course of echographic opacification in the myocardium after experimental injections of contrast agents (hand-agitated Renografin-saline and sonicated sorbitol 70% solutions) into the left main coronary artery. Echographic studies of myocardial cross sections were digitized with an image processing computer using a 128 × 128 resolution matrix. Both stop frame and continuous cycle modes of acquisition were performed. A set of computer programs was developed to extract and analyze time-intensity curves from the digitized images. These included cardiac outline delineation, segmental division, regional intensity computation and exponential curve analysis.

The stop frame method was applied to experimental studies in 17 closed chest dogs during control states and after coronary occlusions. Significant differences were found in the decay half-lives of echo intensity between normal (24 ± 8 seconds) and acutely ischemic (293 ± 165 seconds; $p < 0.001$) myocardium for the Renografin-saline solution. Interobserver reproducibility of the measured half-lives was $r = 0.91$ and standard error of the estimate = 5 seconds. The continuous cycle method of analysis was examined in five closed chest dogs (with up to six injections per dog), applying the sonicated sorbitol 70% solution in only the control state. The mean half-life was 4.2 ± 1.1 seconds.

These computer-based videodensitometric methods might be applied to a wide variety of experimental studies in two-dimensional contrast echocardiography that attempt to quantify myocardial perfusion and function.

There have been several recent reports (1) on quantitative videodensitometry of contrast two-dimensional echocardiograms. DeMaria et al. (2) studied the time course of echo intensities and obtained indicator-dilution type curves by focusing a photometer on the video monitor output of the ultrasound machine. To determine the presence of a left to right shunt, Hagler et al. (3) used a rectangular window in conjunction with a computerized video sampler to measure the intensity over the left and right ventricular outflow tracts. An image digitization technique and placement of a rectangular sampling area over the region of interest was adopted by Meltzer et al. (4) to trace contrast activity in the left ventricle.

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We are currently investigating various aspects of myocardial contrast two-dimensional echocardiography. This paper describes the use of an image processing computer to aid in the quantification of echographic images enhanced by contrast agents. In experiments performed in our laboratory and described elsewhere (5–7), dog myocardium was injected with an intracoronary contrast agent, first during control periods and then after coronary occlusion. It was noticed in the cross-sectional echographic images that opacification of the myocardium varied with the specific site of contrast injection and also with the extent of significantly underperfused myocardium. On the basis of these initial observations, we developed a preliminary procedure for computerized videodensitometric analysis of the spatial and temporal course of contrast-induced alterations of the myocardial echo intensities. The long range objective is to derive indexes that might characterize regional myocardial perfusion.

Methods

Myocardial segmentation in echographic cross sections. For the study of contrast activity, a suitable echographic cross section of the left ventricle was employed and the myocardium was subdivided by a computer program into a number of segments. The segmentation model was developed on the basis of our previous investigations of left ventricular wall motion (8) and on a similar standardization by another group of investigators (9). Epicardium and endocardium of short-axis cross-sectional views were outlined to define the myocardium, which was then subdivided into a predetermined number (usually between 8 and 16) of equiangular segments. The division was accomplished by having the program compute the coordinates of the center of gravity of the epicardial outline, and then referencing the subdivisions using a line joining this center with an internal landmark, such as the junction of the left and right ventricular septum. This basic model was found to be sufficient in most transmural studies of the myocardium for indication of normally or abnormally perfused zones. To examine the pattern of contrast activity in the regional myocardium, this program can also divide the myocardium into concentric subepicardial, midmyocardial and subendocardial layers.

The patterns of contrast opacification across the entire left ventricle could also be investigated with standard short-axis views depicting the principal cross-sectional levels. In this global mapping, we utilized five cross-sectional levels (mitral valve, high papillary muscle, mid-papillary muscle, low papillary muscle and low left ventricular). This was supplemented by radial dissection of each level into 12 equiangular segments, and for special studies, further subdivision into subepicardial, midmyocardial and subendocardial layers.

Data acquisition. Dog myocardium was imaged with a sector scan machine (Advanced Technology Laboratory Mark 300 series) equipped with a 2.25 MHz transducer and 90° mechanical scanner. The echographic images were digitized from the video output of the ultrasound system or from the recorded signal on a videocassette recorder. The latter permitted studies to be reviewed before they were digitized so that redundant sequences would not be stored in the computer system. Our system consisted of a Medical Data Systems A^2 image processing computer with a Nova 4 CPU, 64K words random access memory, 256K words remote image memory, an eight-bit real-time video digitizer, 10MB disk cartridge system and an 80MB storage module.

The video digitizer acquired image data at various expansion factors (between 1 to 4 times magnification of the image) and resolutions of 64 × 64, 128 × 128 and 256 × 256 element images. Typically, electrocardiogram-gated, short-axis two-dimensional views were digitized into 128 × 128 element images with a proportional enlargement over the region of interest. Two modes of image acquisition were considered: continuous cycle and stop frame modes.

In the continuous cycle mode, complete cardiac cycles were digitized. This mode allowed real-time alterations in echo intensities within the cardiac cycle to be analyzed, but it was time consuming and required substantial disk space to store the images. The sampling period depended on the clearance time of the agent. Because of storage and efficiency considerations, this mode of acquisition was practical only in studies with reasonably short contrast clearance times (< 20 seconds).

The stop frame mode refers to accumulation of images frozen at a particular point in time in the cardiac cycle. End-diastolic frames were usually chosen because they were easily located. The time interval for successive frames was determined from the clearance pattern during playback of the video recording. Short intervals (one cardiac cycle between frames) were chosen for the initial rapid inflow and outflow stage, while increasingly longer intervals were selected during the later course of contrast disappearance when fluctuations were generally less pronounced.

In ischemic myocardium where echo contrast persisted for more than 1 minute, the stop frame mode may be used for even longer periods of observation. Each end-diastolic frame had a time marker (obtained from a digital timer superimposed on the echographic images) that was recorded to identify each frame throughout the period of acquisition. Alternatively, gating was accomplished on a cycle to cycle basis using the electrocardiographic signal output provided by the ultrasound instrumentation. Figure 1 shows a condensed sequence of stop frame images digitized from a normal myocardial contrast study. The top left frame is used to establish the background level and is exactly one cardiac cycle before the contrast solution arrives. This sequence is about 60 seconds.

Derivation of myocardial outlines. The derivation of the myocardial outlines must be such that interference from

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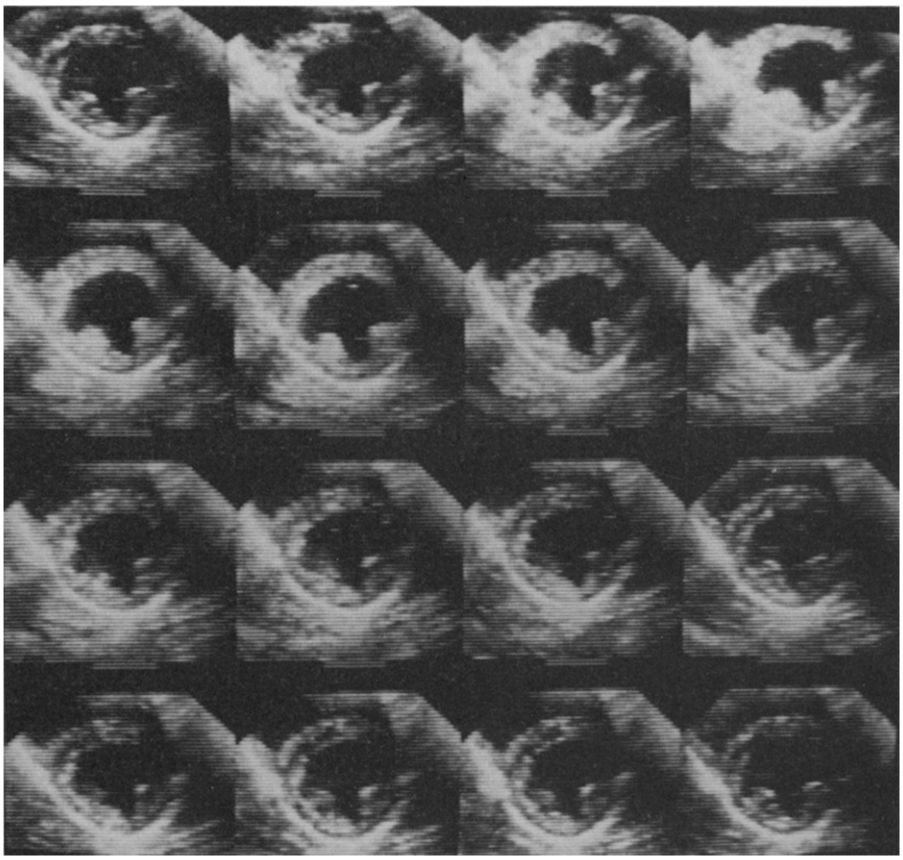

Figure 1. Stop frame mode acquisition of an echocardiographic study of contrast activity in normal dog myocardium. Frame sequence is from **left to right** and top to bottom. The **top left frame** is used to establish background level and is exactly one cardiac cycle before the contrast material arrives. This condensed sequence lasts about 60 seconds.

artifacts and reverberations in the region of interest is minimal. There are often strong specular reflections at the epicardial borders, particularly along the pericardium. These extraneous echoes may bias the sampling accuracy. Thus the endocardial and epicardial outlines were drawn in such a way as to exclude these interfaces; that is, the endocardial area is overestimated while the epicardial area is underestimated. As we were not concerned initially with accurate delineation to simultaneously quantify cardiac function, this interface drawing scheme was different from the leading edge method recently evaluated and proposed in our laboratory for studying regional wall motion (10).

A computer-aided, outlining technique enabled the myocardial silhouette to be drawn in each frame by a human observer. A simple contour detection algorithm produced two sets of 16 points that are placed around the myocardium in a graphics overlay superimposed on the image frame. These points served as rough initial approximations of the endocardial and epicardial walls. The observer then adjusted the points with a set of predefined keys until the points fit the endocardial and epicardial walls. Smoothed outlines (100 points) were produced from these points by the program using cubic B-spline interpolation (11). Sections of the outlines may be edited when the smooth curves have been fitted so that the observer can "fine tune" the fit to the myocardial silhouette. For instance, very intense echoes were sometimes seen in the papillary muscles, and these echos can affect the estimate of the contrast intensity. The observer was able to reshape the outlines to exclude the papillary muscles with a few keystrokes.

Multiple frame analysis. The geometric division of the myocardial silhouette was performed according to the segmentation model guidelines. The computer program first computed the center of gravity of both epicardial and endocardial outlines, and took the coordinate mean of these two points as the overall center of gravity of the myocardium. A fixed axis system was established with this point and an internal landmark was designated by the observer. Examples of internal landmarks are the anterior junction of the right ventricular free wall and the interventricular septum, and the anterior or lateral papillary muscles, whichever is most consistently seen in echographic cross sections throughout the study. Between 8 to 16 segments can be constructed by the program using this fixed axis system. Because this procedure studied echo intensities acquired only in end-diastolic frames, a floating axis system was not essential. In the experimental applications to be described, a 12 segment division was selected so that individual seg-

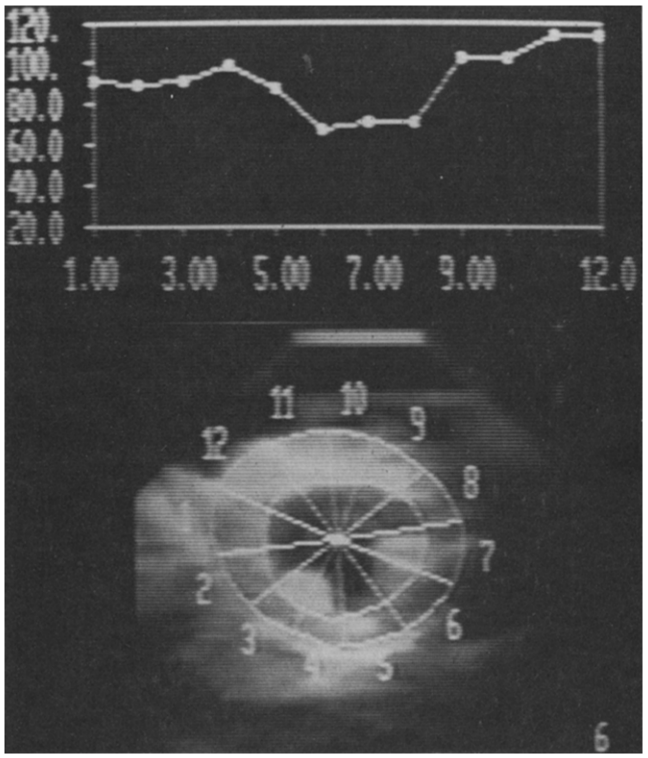

Figure 2. Subdivision of myocardial outlines into 12 segments. A plot of intensity versus segment is also shown.

ments were not too large to understate the gross fluctuations of regional contrast, yet not so small as to prevent assessment of an average intensity.

The mean and standard deviation of the pixel intensities within each of the segments were computed. Also a plot of segmental distribution of the mean intensities was displayed (Fig. 2) to enable the observer to follow the progressive changes of the contrast agent as a simple form of quality control. This procedure was repeated for each of the digitized and outline frames in the two-dimensional echocardiographic study. Finally, time-activity curves were constructed with the help of the recorded time markers.

Analysis of time-activity curves. Figure 3 shows typical time-activity curves in a myocardial segment obtained from stop frame acquisition. Transit time varied with the contrast agent and the mode of injection (for example, volume and pressure of injectate). The upstroke is extremely rapid, with the intensity reaching its peak in almost one quarter of a second. The downslope of the curve was occasionally disrupted by artifacts and contrast intensity often failed to return to its baseline value. Figures 4 and 5 are examples of curves that were derived from continuous cycle acquisition. Note the rapid cardiac oscillations that are superimposed on the curve; peaks were seen at end-diastole and dips at end-systole. This cyclic variation was absent in the curves derived from stop frame mode because at end-diastole, the myocardium is almost nearly in the same position at the time of acquisition.

In most cases, a single exponential function was fitted to the downslope of the time-activity curve. Before that, the baseline intensity was subtracted from all points in the curve. This subtraction forces the exponential to decay to the baseline value rather than the absolute zero value of the curve. From the fit, a decay rate constant was computed and subsequently converted to a half-life. Exponential fitting was accomplished with a least squares fit to the data points of the curve. Half-life T(½) was computed from the formula:

$$T(½) = \ln 2/\text{decay constant},$$

where ln = natural logarithm.

Results

We summarize the results of the experimental applications of stop frame acquisition and the continuous cycle mode methods. The detailed experimental description of the

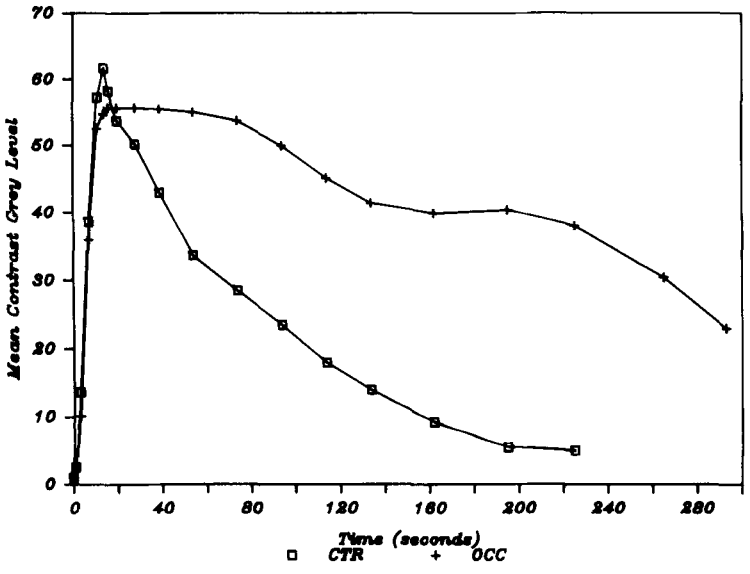

Figure 3. Time-activity curves obtained from normal (**squares**) and ischemic (**plus signs**) myocardium. Half-life of the normal control (CTR) curve is about 30 seconds, while half-life of the ischemic curve after coronary occlusion (OCC) is longer than 2 minutes.

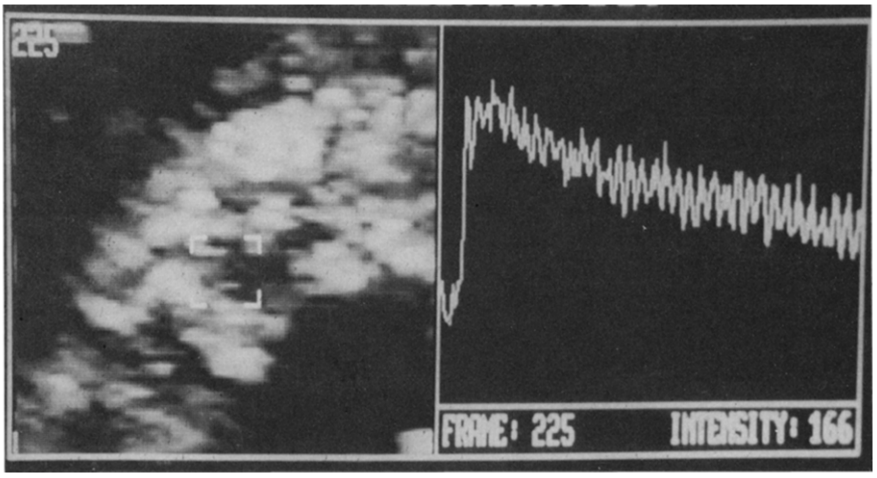

Figure 4. Analysis of the last frame of an echocardiographic study digitized in continuous cycle mode of acquisition. A rectangular window is placed between epicardial and endocardial borders in each of the 225 frames in the study.

stop frame method is presented elsewhere (7) and the continuous cycle mode description will be presented in a forthcoming paper.

Stop frame method. For the application of the stop frame method, preliminary experiments with the injection of hand-agitated solution of Renografin-saline before and after coronary occlusion were performed in 17 dogs. In this example, the solution was injected through the left main coronary artery, or into the left anterior descending branch distal to an intracoronary balloon occlusion. The digitized two-dimensional frames covered a time period of 1 to 2 minutes for left main coronary injections, and 4 to 8 minutes for the anterior descending artery injections. Initially, the last two end-diastolic frames before the contrast injection were digitized to establish a baseline for the myocardial intensity. They were followed by successive end-diastolic frames after the contrast injection for about eight cardiac cycles. A progressive increase then occurred in intervals between frames in the later stage of the contrast clearance period. The digitized frames were then viewed in a cine loop to check for stability of the short-axis images in relation to each other and to observe the time course of contrast opacification in a condensed format. Cardiac outline delineation and time-intensity curves were obtained as described previously in this report.

Significant differences were found in the clearance patterns of the Renografin-saline solution in normal myocardium versus those in dogs with induced coronary occlusion and myocardial ischemia. Mean half-lives in selected but comparable segments of interest were 24 ± 8 seconds in the control studies and 294 ± 165 seconds (probability [p] < 0.001) for acute ischemia distal to a coronary occlusion (Fig. 3). Interobserver reproducibility of the measured half-lives was $r = 0.91$ and standard error of the estimate = 5

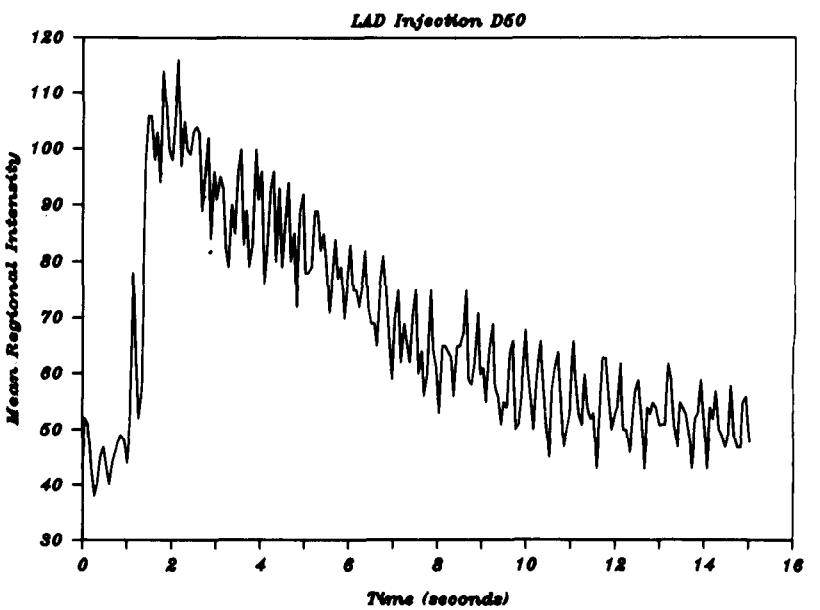

Figure 5. Time-activity curve obtained from normal myocardium using continuous cycle acquisition and analysis. Note rapid oscillations associated with the cardiac cycle.

seconds. The long clearance time in the control state is typical of hand-agitated contrast agents that are known to contain a heterogeneous mixture of microbubbles ranging from very small (and potentially capable of microcirculatory transit) to as large as 50 μ in diameter.

Continuous cycle method. In the application of the continuous cycle method, a solution of sorbitol 70% was agitated with a sonicator that vibrates at ultrasonic frequencies. This method of agitation produced smaller and more uniform microbubbles (about 6 μ in diameter). The sonicated solution was injected into the left main coronary artery of five closed chest healthy dogs each with about six injections. The average half-life from seven of these injections was calculated to be 4.2 $\pm$ 1.1 seconds ($p < 0.001$) in the normally perfused myocardium (Fig. 5). This compares favorably with other indicator-dilution data on myocardial transit studies.

Discussion

Limitations of the method. The precision of numerical quantities extracted from a digitized echographic image can be influenced by the properties of the sampling system, such as axial and lateral resolution of the imaging system, and other factors such as transducer side-lobe energy, gain control settings, depth-gain compensation, dynamic range and output signal processing. Thus, steps must be taken to minimize these influences because nearly every time-activity curve is distorted by the recording system used to procure it.

Noise is abundant in echographic images. We applied digital filters to smooth out local intensity scatter in the spatial domain (within frames) and in the time domain (across frames). Such smoothing routines suppress the high-frequency noise components (12) and leave the low frequency detail of the images intact. Here the term "frequency components" refers to the digitized video signal and not the ultrasound beam frequencies. The smoothed images are blurred and may not be pleasing to the human eye. However, with the reduction in noise, the random scatter of the echo intensities is also reduced. There is an inherent danger (due to respiration or whole heart motion, for example) in smoothing across frames because mismatched myocardial silhouettes may create regions of artificial intensities rather than reduce the scatter. For this reason, we decided to use, as background levels, only the mean intensities of the two end-diastolic frames before injection and not perform baseline image smoothing. Later on, we smoothed the time-intensity curves instead because the intensities in the curves would already be corrected for motion by the segmental division algorithm. In an optimal setting, digital smoothing could at best remove the noise inherent in the imaging system. We are still faced with the problem of specular reflection which can seriously affect the intensity measurements in myocardial contrast two-dimensional echocardiography. In all of our studies, we implemented a drawing technique that excluded these specular echoes from the endocardial and epicardial interfaces and the papillary muscles.

The problem with digitizing images from the video output of the ultrasound scanner or the playback signal from a videocassette recorder is that the digitized images have a decreased dynamic range. This is because commercial ultrasound instrumentation processes echographic images for display in a manner that makes these images pleasing to the human eye. Because the eye cannot readily differentiate more than 16 shades of gray, the images are usually transformed to just 16 display shades. This compressed dynamic range of the ultrasound machines hampered the rigorous quantitative investigation of the time course of the contrast agent.

To improve the dynamic range information of the images, the echo signal will have to be digitized before depth gain control and output processor stages, that is, after radio frequency detection. But the problem is that the functions of the ultrasound scanner (such as, time gain compensation and scan converter) will have to be duplicated in software. As a compromise, the images can be tapped at the output of the scan controller. We are currently working on a video interface board that allows the digital image from the scan controller to be transferred directly to the remote image memory of the computer. This should produce a raw image with an increased dynamic range.

Beam attenuation along various scan directions is not uniform because each beam traverses unequal tissue material. Hence, echo intensities reflected from acoustically similar tissue layers along two beam directions at a constant depth may not be comparable. This is typical of commercial machines that employ constant depth gain compensation. Rational gain compensation (13) has been suggested to compensate for attenuation by blood and myocardium. In this method, separate gain profiles are produced for each beam direction by comparing the echo amplitudes with preset threshold levels for blood and myocardial backscatter.

Microbubble enhancement. Myocardial enhancement is most clearly discerned in echographic images when microbubble perturbation is at its peak. This phenomenon takes the form of an intensified area behind the true position of an anterior layer of microbubbles. The intensity and spread of this area are proportional to the size and density of the microbubbles flowing through the region of interest. As a result, large and dense microbubbles (> 50 μ) tend to produce an intense layer of artifactual echoes.

This phenomenon stems mainly from the acoustic impedance mismatch between myocardial tissue and the air-filled microbubbles. Ultrasound travels in myocardial tissue (1,580 m/s) at almost five times its velocity in an air-filled medium (330 m/s). When the beam traverses the microbubble from diverging angles of incidence, it is invariably refracted to-

ward the center of the microbubble. Hence, there is a focusing effect as the beam converges. With a large number of microbubbles, the region of interest becomes an ensemble of random spherical scatterers that act in tandem to create the enhancement area behind the region of interest.

Clearly, it is advantageous to inject microbubbles of small dimensions and densities to reduce the observed intensification. Even with small bubbles, beam focusing may be pronounced occasionally because of the larger curvature of the microbubbles, but this is balanced by the reduced path length of the beam in the microbubbles. Also, the exclusion of the specular layers of the endocardium and epicardium in the drawing method helped eliminate a portion of this enhancement region.

Time-activity curves. The choice of the exponential model to fit the raw data was made on the basis of the similarity of this study to classic indicator-dilution techniques for determining blood flow. It should be pointed out that the assumptions underlying indicator-dilution theory are almost certainly not satisfied for the contrast agents used in the present study. Thus, we view the derived half-life as an index of perfusion, rather than a quantity from which we could calculate the absolute perfusion rate. Even with this restricted interpretation, the use of a model that may not be representative of blood flow is an important limitation of our method. However, these results support the existence of a correlation between the washout rate of echo contrast material as measured by our technique and myocardial perfusion. Further, the reduction of half-life as the bubble size is made smaller and the bubble homogeneity is improved, supports our interpretation of the frequently observed failure of the curve to plateau at the preinjection level after washout.

Although much work remains to be done to improve the contrast agents and better understand the physics of the image generation process as just described, we believe that the present algorithms account for the major features of the washout phenomenon, allowing for meaningful correlation of a derived perfusion index with independent measurements of myocardial perfusion. Future refinements in the analysis that could be made, beyond improvement of the physical accuracy with which contrast concentration is measured, include modification of the segmentation model to take into account the heterogeneity of bubble sizes, and to separate the input (injection) curve from the myocardial curve to remove the effect of variations of injection rate and duration.

Conclusion. We developed a computerized videodensitometric method for analysis of myocardial contrast two-dimensional echocardiography. The objectives were to derive time-activity curves from myocardial segments during an intracoronary (or alternate site) injection of an echo contrast agent, and analyze these curves to make inferences about the distribution and extent of myocardial perfusion. Changes in myocardial blood flow before and after coronary occlusion or other interventions might then be evaluated with computerized videodensitometry. It is anticipated that further development of methods for myocardial contrast echocardiography and advanced segmental models of the cardiac anatomy will eventually allow mapping of the left ventricle to characterize and compare patterns of both regional cardiac function and myocardial perfusion.

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